

the amended claims are set forth herebelow, in clean form and as required by 37 C.F.R. § 1.121(c)(1)(i). Pursuant to the requirements of 37 C.F.R. § 1.121(c)(1)(ii), another version of each rewritten claim is submitted herewith at Exhibit Tab A, marked up to show all the changes relative to the previous version of that claim.

Applicants also submit herewith: (1) a Petition for Extension of Time, requesting that the time period for responding to the Office Action be extended for a period of two months (*i.e.*, from APRIL 15, 2002 up to and including JUNE 15, 2002), accompanied by the appropriate fee; and (2) an Amendment Transmittal letter, accompanied by the appropriate fee. It is believed that no additional fees are required for these submissions. However, should the U.S. Patent and Trademark Office determine that any additional fee is required or that any refund is owed for this application, please charge the required fee(s) and/or credit the refund(s) owed to our Deposit Account No. 04-0100.

Please amend the application as follows:

IN THE CLAIMS:

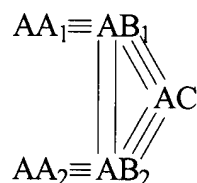
~~Cancel~~ claims 4 and 36 without prejudice or admission.

~~Amend~~ claims 2, 5, 9, 13, 15, 18-19, 23, 27, 34, 37, 41 and 45

without prejudice or admission, as indicated in the attached Exhibit A, so that those claims read as follows:

2. (Twice Amended) A method of inhibiting osteoclastogenesis

comprising the steps of administering to a patient an amount of an inhibitor effective to inhibit osteoclastogenesis, wherein the inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB₁ is a moiety having a first functional group forming a covalent linkage with one terminus of AC, a second functional group forming a covalent linkage with AB₂ and a third functional group forming a covalent linkage with AA₁ ;

B1
AB₂ is a moiety having a first functional group forming a covalent linkage with the second terminus of AC, a second functional group forming a covalent linkage with AB₁ and a third functional group forming a covalent linkage with AA₂;

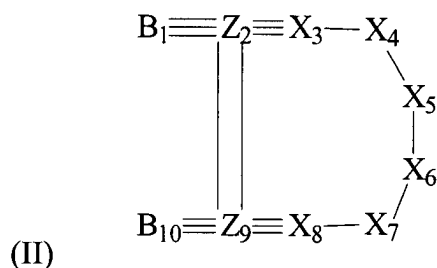
AA₁ is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB₂;

AA₂ is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB₂;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

B2
5. (Amended) The method of Claim 4 wherein the inhibitor has the formula:



wherein:

B₁ and B₁₀ are each independently a peptide of 1-6 amino acids at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

B2
Z₂ is a moiety forming a covalent linkage with B₁, X₃ and Z₉;

Z₉ is a moiety forming a covalent linkage with B₁₀, X₈ and Z₂;

X₃ is absent or a hydrophilic amino acid;

X₄ is a hydrophobic amino acid;

X₅ is a hydrophobic amino acid;

X₆ is a hydrophobic amino acid;

X₇ is a hydrophobic or hydrophilic amino acid;

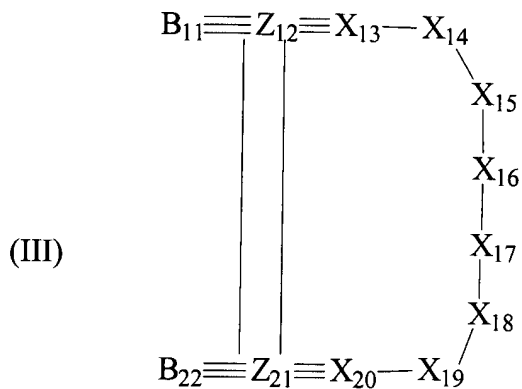
X₈ is a hydrophobic or hydrophilic amino acid;

"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

B3
9. (Amended) The method of Claim 4, wherein the inhibitor has the formula:



wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{12} is a moiety forming a covalent linkage with B_{11} , X_{13} and Z_{21} ;

Z_{21} is a moiety forming a covalent linkage with B_{22} , X_{20} and Z_{12} ;

X_{13} is absent or hydrophobic amino acid;

X_{14} is absent or hydrophilic amino acid;

X_{15} is a hydrophilic or hydrophobic amino acid;

X_{16} is a hydrophilic amino acid;

X_{17} is absent or a hydrophobic amino acid;

B3
X₁₈ is a hydrophilic amino acid;

X₁₉ is a hydrophilic amino acid;

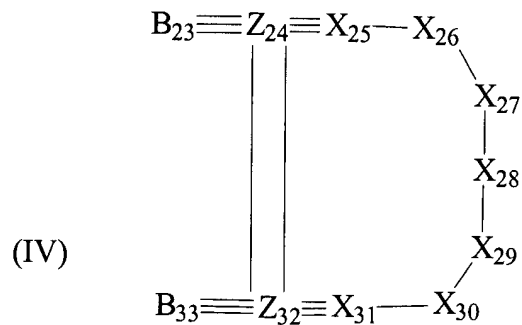
X₂₀ is a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

B4
13. (Amended) The method of Claim 4, wherein the inhibitor has the formula:



wherein:

B₂₃ and B₃₃ are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

B4
Z₂₄ is a moiety forming a covalent linkage with B₂₃, X₂₅ and Z₃₂;

Z₃₂ is a moiety forming a covalent linkage with B₃₃, X₃₁ and Z₂₄;

X₂₅ is absent or a hydrophilic amino acid;

X₂₆ is a hydrophilic amino acid;

X₂₇ is a hydrophilic amino acid;

X₂₈ is a hydrophilic amino acid;

X₂₉ is a hydrophilic amino acid;

X₃₀ is absent or a hydrophilic amino acid;

X₃₁ is absent or a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

B5
15. (Amended) The method of Claim 14, wherein:

B₂₃ and B₃₃ are each independently Tyr or Phe;

Z₂₄ and Z₃₂ are each Cys;

X₂₅ is absent or Arg;

X₂₆ is Lys;

X_{27} is Glu;

X_{28} is Leu, Pro or Met;

X_{29} is Gly;

X_{30} is absent or Gln;

X_{31} is absent or Val;

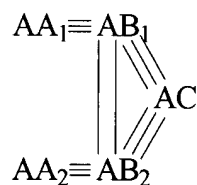
"-" is an amide linkage;

"=" is a disulfide linkage; and

" \equiv " is an amide linkage.

18. (Twice amended) A method of treating patients who have diseases

characterized by bone loss comprising the step of administering to said patient an amount of an inhibitor effective to inhibit such bone loss, wherein said inhibitor is a compound having the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

24 AB₁ is a moiety having a first functional group forming a covalent linkage with one terminus of AC, a second functional group forming a covalent linkage with AB₂ and a third functional group forming a covalent linkage with AA₁;

AB₂ is a moiety having a first functional group forming a covalent linkage with the second terminus of AC, a second functional group forming a covalent linkage with AB₁ and a third functional group forming a covalent linkage with AA₂;

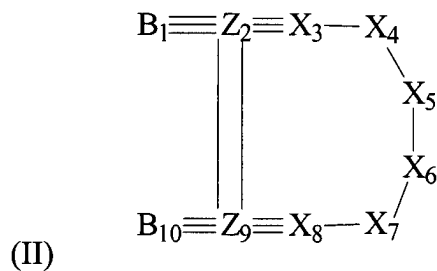
AA₁ is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB₁;

AA₂ is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB₂;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

19. (Amended) The method of claim 18 wherein the compound has the formula:



wherein:

B_1 and B_{10} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_2 is a moiety that is forming a covalent linkage with B_1 , X_3 and Z_9 ;

Z_9 is a moiety that is forming a covalent linkage with B_{10} , X_8 and Z_2 ;

X_3 is absent or a hydrophilic amino acid;

X_4 is a hydrophobic amino acid;

X_5 is a hydrophilic amino acid;

X_6 is a hydrophilic amino acid;

X_7 is a hydrophobic or hydrophilic amino acid;

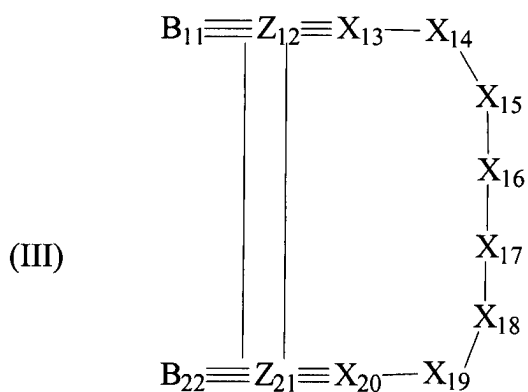
X_8 is a hydrophobic or hydrophilic amino acid;

"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

23. (Amended) The method of claim 18 wherein the compound has the formula:



wherein:

B_{11} and B_{22} are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z_{12} is a moiety forming a covalent linkage with B_{11} , X_{13} and Z_{21} ;

Z_{21} is a moiety forming a covalent linkage with B_{22} , X_{20} and Z_{12} ;

X_{13} is absent or hydrophobic amino acid;

X_{14} is absent or a hydrophilic amino acid;

X_{15} is a hydrophilic or hydrophobic amino acid;

X_{16} is a hydrophilic amino acid;

X_{17} is absent or a hydrophobic amino acid;

X_{18} is a hydrophilic amino acid;

X_{19} is a hydrophilic amino acid;

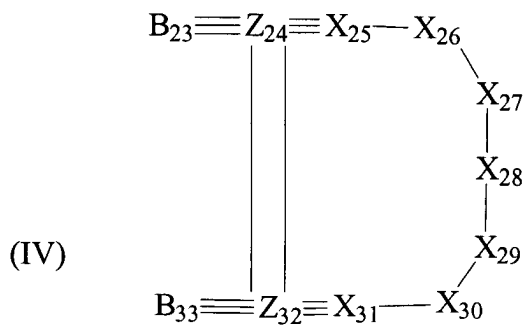
X_{20} is a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

27. (Amended) The method of claim 18 wherein the compound has the formula:



wherein:

B₂₃ and B₃₃ are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z₂₄ is a moiety of forming a covalent linkage with B₂₃, X₂₅ and Z₃₂;

Z₃₂ is a moiety of forming a covalent linkage with B₃₃, X₃₁ and Z₂₄;

X₂₅ is absent or a hydrophilic amino acid;

X₂₆ is a hydrophilic amino acid;

X₂₇ is a hydrophilic amino acid;

X₂₈ is a hydrophobic amino acid;

X₂₉ is a hydrophobic amino acid;

X₃₀ is absent or a hydrophobic amino acid;

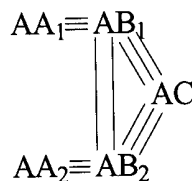
X₃₁ is absent or a hydrophobic amino acid;

"-" is an amide, a substituted amide or an isostere of amide;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

34. (Twice amended) A method of inhibiting bone resorption comprising the step of administering to a patient an amount of an inhibitor effective to inhibit bone resorption, wherein said inhibitor has the formula:



(I)

wherein:

AC is a peptide of 3-18 amino acid residues which corresponds in primary sequence to a binding loop of TNF-R(I), and which may optionally contain one or more amino acid substitutions, or an analogue thereof wherein at least one amide linkage is replaced with a substituted amide or an isostere of amide;

AB₁ is a moiety having a first functional group forming a covalent linkage with one terminus of AC, a second functional group forming a covalent linkage with AB₂ and a third functional group forming a covalent linkage with AA₁ ;

AB₂ is a moiety having a first functional group forming a covalent linkage with the second terminus of AC, a second functional group forming a covalent linkage with AB₁ and a third functional group forming a covalent linkage with AA₂;

AA₁ is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB₂;

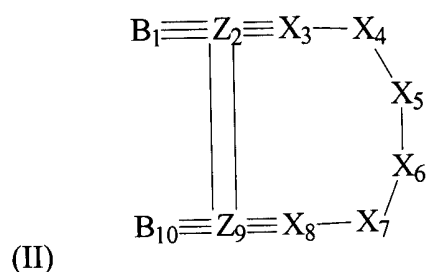
AA₂ is a moiety having hydrophobic properties and a functional group forming a covalent linkage with the third functional group of AB₂;

B9
"=" is a covalent linkage; and

"≡" is a covalent linkage.

37. (Amended) The method of Claim 36 wherein the inhibitor has the

B10
formula:



wherein:

B₁ and B₁₀ are each independently a peptide of 1-6 amino acids at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z₂ is a moiety forming a covalent linkage with B₁, X₃ and Z₉;

Z₉ is a moiety forming a covalent linkage with B₁₀, X₈ and Z₂;

X_3 is absent or a hydrophilic amino acid;

X_4 is a hydrophobic amino acid;

X_5 is a hydrophobic amino acid;

X_6 is a hydrophobic amino acid;

X_7 is a hydrophobic or hydrophilic amino acid;

X_8 is a hydrophobic or hydrophilic amino acid;

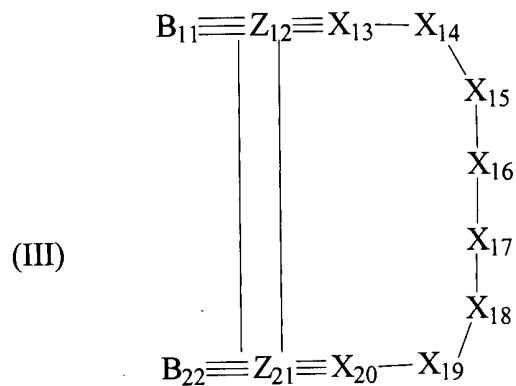
"-" is an amide, substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

41. (Amended) The method of Claim 36, wherein the inhibitor has the

formula:



wherein:

B₁₁ and B₂₂ are each independently a peptide of 1-6 amino acids, at least one of which is a hydrophobic amino acid, an aromatic moiety or a heteroaromatic moiety;

Z₁₂ is a moiety forming a covalent linkage with B₁₁, X₁₃ and Z₂₁;

Z₂₁ is a moiety forming a covalent linkage with B₂₂, X₂₀ and Z₁₂;

X₁₃ is absent or hydrophobic amino acid;

X₄ is absent or hydrophilic amino acid;

X₁₅ is a hydrophilic or hydrophobic amino acid;

X₁₆ is a hydrophilic amino acid;

X₁₇ is absent or a hydrophobic amino acid;

X₁₈ is a hydrophilic amino acid;

X₁₉ is a hydrophilic amino acid;

X₂₀ is a hydrophilic amino acid;

"-" is an amide, a substituted amide or an isostere of amide thereof;

"=" is a covalent linkage; and

"≡" is a covalent linkage.

45. (Amended) The method of Claim 36, wherein the inhibitor has the formula:

